Faraday Discussions

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Journal:	*Faraday Discussions*
Manuscript ID	FD-ART-02-2023-000045.R1
Article Type:	Paper
Date Submitted by the Author:	14-Mar-2023
Complete List of Authors:	Shibuya, Akito; Tottori Daigaku - Tottori Campus Ishisaka, Yui; Tottori Daigaku - Tottori Campus Saito, Asuka; Tottori Daigaku - Tottori Campus Kato, Moeko; Tottori Daigaku - Tottori Campus Manmode, Sujit; Indian Institute of Science Education & Research, Department of Chemistry Komatsu, Hiroto; Tottori Daigaku - Tottori Campus Rahman, Md Azadur; Tottori University, Chemistry and biotechnology Sasaki, Norihiko; Tottori Daigaku - Tottori Campus Itoh, Toshiyuki; Toyota Physical and Chemical Research Institute, ; Tottori University Graduate School of Engineering Faculty of Engineering, Nokami, Toshiki; Tottori University - Tottori Campus, Chemistry and Biotechnology

ARTICLE

Electrochemical Synthesis of the Protected Cyclic (1,3;1,6)-β-Glucan Dodecasaccharide

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Akito Shibuya,[a] Yui Ishisaka,[b] Asuka Saito,[b] Moeko Kato,[b] Sujit Manmode,[a] Hiroto Komatsu,[c] Md Azadur Rahman,[a] Norihiko Sasaki,[a,d] Toshiyuki Itoh, [a,d] and Toshiki Nokami*[a,d]

Automated electrochemical assembly is an electrochemical method to synthesise middle–sized molecules, including linear oligosaccharides, and some linear oligosaccharides can be electrochemically converted into the corresponding cyclic oligosaccharides effectively. In this study, the target cyclic oligosaccharide is a protected cyclic (1,3;1,6)-β-glucan dodecasaccharide, which consists of two types of glucose trisaccharides with β-(1,3)- and β-(1,6)-glycosidic linkages. The formation of the protected cyclic dodecasaccharide was confirmed by the electrochemical one-pot dimerisation–cyclisation of the semi-circular hexasaccharide. The yield of the protected cyclic dodecasaccharide was improved by using a stepwise synthesis via the linear dodecasaccharide.

Introduction

Electrochemical transformations of small molecules have been used as a powerful set of tools in organic synthesis for many decades.[1] Recent progress in this area has enabled the synthesis of complex molecules such as natural products,[2] peptides,[3] and oligosaccharides.[4] We have been interested in the automated synthesis of oligosaccharides using electrochemical methods and have developed a method named 'automated electrochemical assembly' (AEA), which is based on electrochemical generation of a glycosylation intermediate and its subsequent coupling with alcohols, including oligosaccharides.[5]

Cyclic oligosaccharides such as cyclodextrins (CDs), which contain 1,4-α-linked D-glucopyranose, have attracted the interest of researchers for more than a century because of their unique structures and properties.[6] To our knowledge, δ-CD (nonasaccharide) is the largest CD that has been chemically synthesised to date.[7] With regard to cyclic oligosaccharides containing other glycosidic linkages and monosaccharides, cyclic oligo-1,6-β-D-glucosamines up to the heptasaccharide were synthesised by the Nifantiev group[8] and our group.[9] More recently, our group reported the synthesis of cyclic oligo-1,4-α-*N*-acetylglucosamine 'cyclokasaodorin' through an electrochemical polyglycosylation–isomerisation–cyclisation process.[10] In this case, however, only hexasaccharide and heptasaccharide were obtained. Therefore, the chemical synthesis of large cyclic oligosaccharides remains challenging.

We then focused on a natural oligosaccharide isolated from *Bradyrhizobium japonicum* MTCC120.[11] The oligosaccharide has a cyclic dodecasaccharide structure that consists of two types of glucose trisaccharides with β-(1,3)- and β-(1,6)-glycosidic linkages. Here, we report the electrochemical synthesis of the protected cyclic (1,3;1,6)-β-glucan dodecasaccharide as a potential precursor of the natural cyclic dodecasaccharide.

Results and discussion

Retrosynthetic analysis

Protected cyclic dodecasaccharide **1** has a symmetric structure that consists of β-(1,3)- and β-(1,6)-glycosidic linkages (Fig. 1). Thus, we envisioned that an ideal approach to synthesise protected cyclic dodecasaccharide **1** would be through dimerisation of the semi-circular hexasaccharide building block **2** followed by cyclisation in the same pot. These semi-circular hexasaccharides **2a** and **2b** were considered suitable building blocks because they both have a protecting-group-free hydroxy group (**2a**: 3-OH, **2b**: 6-OH) and thioaryl (SAr, **2a**: Ar = 4-FC_6H_4, **2b**: Ar = 4-ClC_6H_4) leaving group at the anomeric position (C-1). To examine the hypothesis, we synthesised the semi-circular hexasaccharide building block **2a**, bearing two β-(1,3)-glycosidic linkages and three β-(1,6)-glycosidic linkages.[12] Although **2a** was prepared under the electrochemical conditions, its total yield was very low. Moreover, **2a** had a protecting-group-free 3-OH which must be less reactive than the 6-OH group. Therefore, we designed semi-circular hexasaccharide **2b** as a building block equipped with a protecting-group-free 6-OH. Semi-circular hexasaccharide **2b** could be disconnected to disaccharide building block **3** and tetrasaccharide building block **4b** with β-(1,6)-glycosidic and β-

[a] Graduate School of Engineering, Tottori University
[b] Graduate School of Sustainable Science, Tottori University
[c] Department of Chemistry and Biotechnology, Faculty of Engineering, Tottori University
[d] Centre for Research on Green Sustainable Chemistry, Faculty of Engineering, Tottori University

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

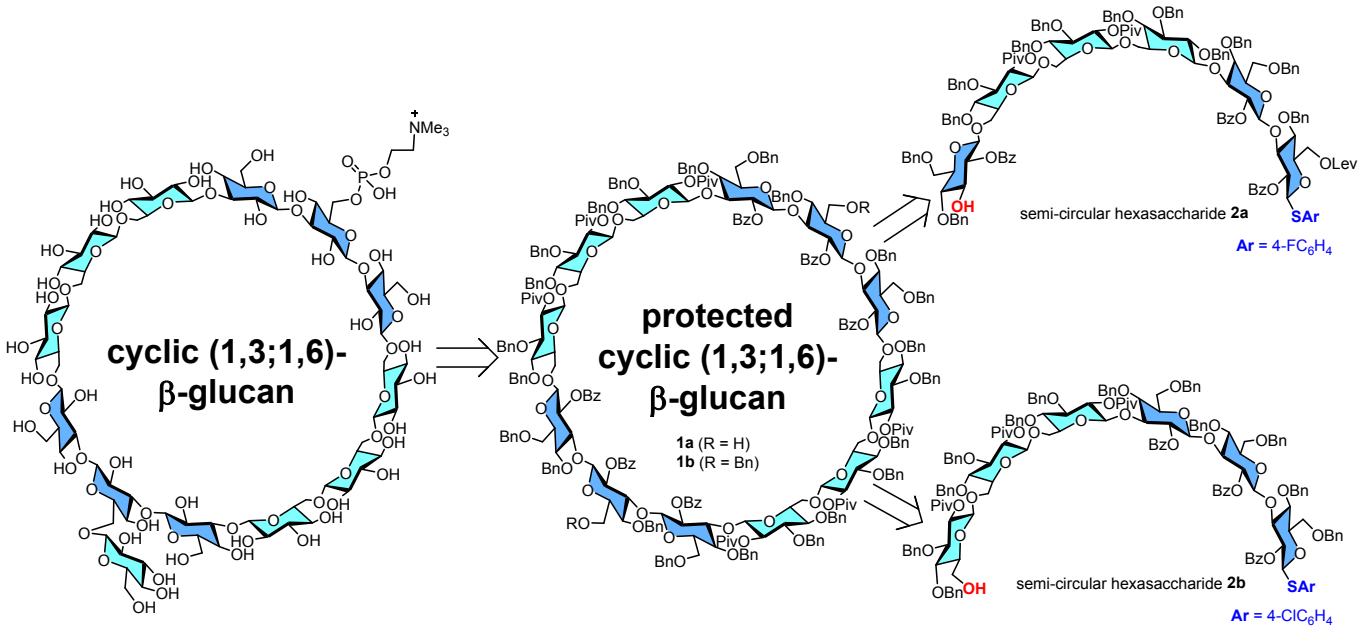


Fig. 1 Semi-circular hexasaccharides building blocks for the protected cyclic (1,3; 1,6)-β-glucan.

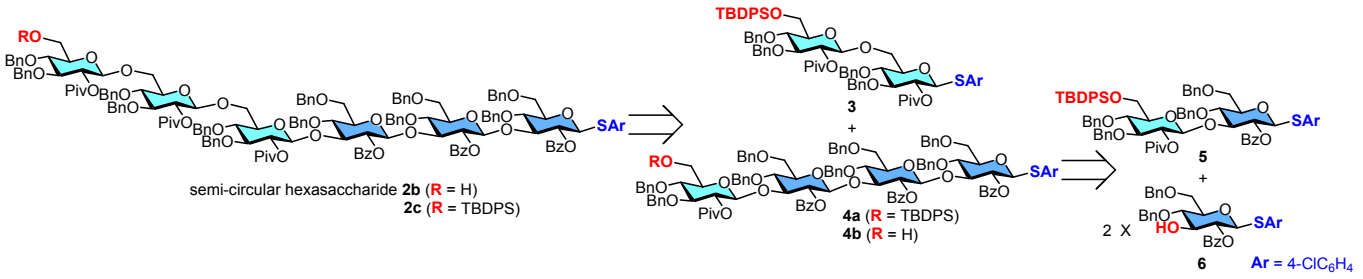


Fig. 2 Retrosynthesis of semi-circular hexasaccharide **2b** and its building blocks **3**-**6**.

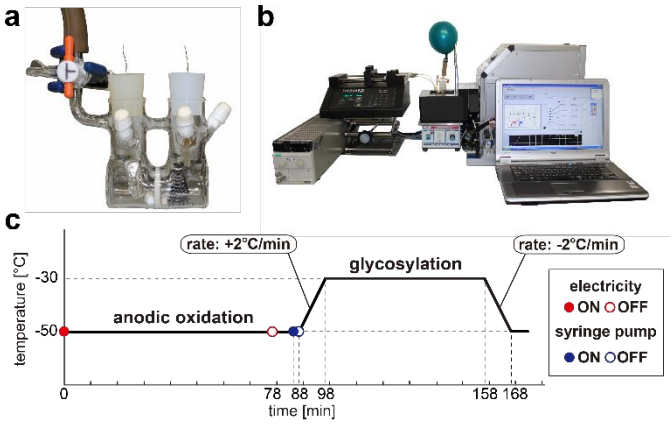


Fig. 3 Devises for automated electrochemical assembly. a) Divided electrolysis cell equipped with platinum plate cathode and carbon fibre anode. b) The 1st generation automated electrochemical synthesizer. c) Schedule of synthesizer for a single cycle.

(1,3)-glycosidic linkages, respectively (Fig. 2). Tetrasaccharide **4a**, as the precursor of **4b** derived from disaccharide building block **5**, with a β-(1,3)-glycosidic linkage, and two equivalents of monosaccharide building block **6**, equipped with the protecting-group-free 3-OH.

Synthesis of the disaccharide building blocks

Automated electrochemical assembly was performed using a middle-size divided electrolysis cell (15 mL for anode and cathode) equipped with carbon fiber anode and platinum plate cathode under argon atmosphere (Fig. 3a). The electrolysis was placed in the cooling bath of the 1st generation automated electrochemical synthesizer (Fig. 3b). The synthesizer was composed of chiller with a cooling bath, stable direct current (DC) power supply, syringe pump, magnetic stirrer, and personal computer (PC), and these devices were controlled by LabVIEW installed in the notebook PC. The schedule of a single cycle was shown in Fig. 3c. The DC power supply applied a constant current (13 mA, 1.05 F/mol) during the anodic oxidation and the electrolysis time (4677 sec = ca 78 min) depended on both reaction scale (0.60 mmol) and current value

(13 mA). The chiller kept two temperatures -50°C and -30°C during anodic oxidation and glycosylation, respectively. In some cases, we switched off the chiller before quenching of the reaction and raised the temperature up to 0°C to complete the glycosylation. Two gastight syringes were filled with solution of a building block and solvent for anodic chamber and cathodic chamber, respectively. They were set to the syringe pump and solutions were added at rate 1.0 mL/min after electrolysis.

Synthesis of the disaccharide building blocks

Monosaccharide building blocks **6**, **7a**, and **7b** were prepared from D-glucose pentaacetate according to the reported procedures (Fig. 4). Disaccharide building block **3**, with a β-(1,6)-glycosidic linkage, was prepared using AEA between **7a** and **7b** in the presence of tetrabutylammonium triflate (Bu_4NOTf) as an electrolyte. Glycosyl dioxalenium ion intermediate **8** was generated by anodic oxidation of **7a** under constant current conditions at -50°C. Subsequent coupling of **8** and building block **7b** (1.2 equiv.) afforded disaccharide **3** in 81% yield. This is a standard AEA protocol, and the details of reaction conditions and structures of possible intermediates have been omitted from the following figures (see the ESI for details of reaction conditions). Although disaccharide building block **5**, with a β-(1,3)-glycosidic linkage, was also prepared using AEA of **7a** and **6** (1.2 equiv.) in 85% yield, the one-pot synthesis of tetrasaccharide **4a** from monosaccharide building block **7a** using AEA with three cycles was sluggish.

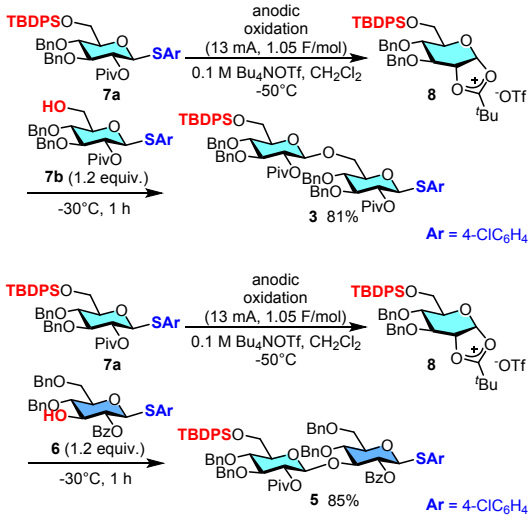
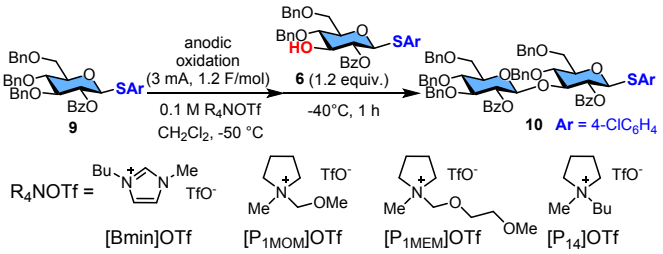


Fig. 4 Synthesis of disaccharide building blocks **3** and **5**.

Optimisation of electrolyte for AEA

The electrolyte for AEA was optimised using the electrochemical formation of β-(1,3)-glycosidic linkages using monosaccharides **9** and **6** (1.2 equiv.) as model building blocks (Table 1). Whereas the use of tetraethylammonium triflate (Et_4NOTf) afforded disaccharide **10** in moderate yield (entry 1), Bu_4NOTf, which has been used as a standard electrolyte for AEA, gave the product **10** in good yield (entry 2). We also examined the use of ionic liquids (entries 3–6). The initial voltage of anodic oxidation was significantly influenced by the electrolyte; however, there was no clear relationship between the initial voltage and the product yield. Amongst these ionic liquids, 1-butyl-1-methylpyrrolidinium triflate ($[P_{14}]OTf$) afforded the desired disaccharide **10** in the highest yield (entry 6). Therefore, we used ionic liquid $[P_{14}]OTf$ as an electrolyte in the following glycosylation reactions. It has not been clarified why $[P_{14}]OTf$ gave the best yield; however, oxidation potential (E_{ox}) of monosaccharide building block **9** measured with $[P_{14}]OTf$ (E_{ox} = 1.67 V vs. SCE) was slightly lower than that measured with Bu_4NOTf (E_{ox} = 1.70 V vs. SCE). We assume that electrolytes may influence the structure of electrical double layer and the process of single electron transfer.

Table 1 Optimisation of electrolyte of AEA



entry	electrolyte	initial voltage[a]	yield[b]
1	Et_4NOTf	26 V	61
2[a]	Bu_4NOTf	14 V	79
3[a]	[Bmim]OTf	59 V	70
4	$[P_{1MOM}]OTf$	93 V	81
5	$[P_{1MEM}]OTf$	26 V	89
6	$[P_{14}]OTf$	51 V	97

[a]Inter-electrode voltage. [b]Determined by NMR.

Synthesis of the tetrasaccharide building block

The synthesis of tetrasaccharide **4a**, with three β-(1,3)-glycosidic linkages, from disaccharide **5** was carried out using AEA with two consecutive glycosylation cycles with monosaccharide building block **6** (1.0 equiv). The process was still challenging; however, performing the reaction sequence in the presence of $[P_{14}]OTf$ gave a slightly better yield than with Bu_4NOTf (Fig. 5). Deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group of **4a** was achieved successfully in the presence of hydrogen fluoride pyridine complex (HF•pyridine) to obtain tetrasaccharide building block **4b**, equipped with a protecting-group-free 6-OH, in 83% yield.

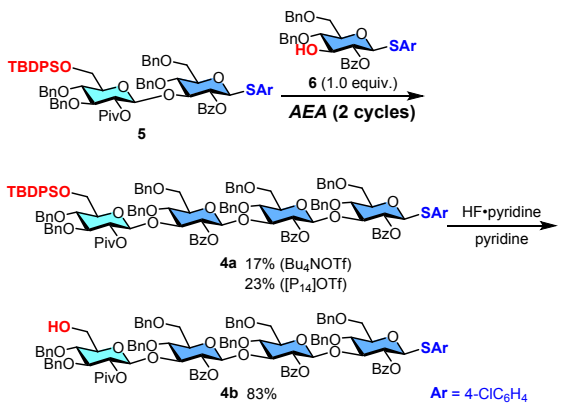


Fig. 5 Synthesis of tetrasaccharide building block **4b**.

Synthesis of the semi-circular hexasaccharide and its dimerisation

Semi-circular hexasaccharide building block **2b** was prepared using AEA and subsequent TBDPS deprotection (Fig 6). Disaccharide **3** and tetrasaccharide **4b** (1.2 equiv.) were assembled to prepare TBDPS-protected semi-circular hexasaccharide **2c** in the presence of $[P_{14}]OTf$ as an electrolyte. Deprotection of the TBDPS group at 6-OH was carried out under the standard reaction conditions with HF•pyridine, and the desired semi-circular hexasaccharide **2b** was obtained in 86% yield. Thus-obtained **2b**, equipped with a protecting-group-free 6-OH, was used as a building block in the one-pot dimerisation–cyclisation process to synthesise protected cyclic dodecasaccharide **1b** (Scheme 1). Although the yield of **1b** was very low (3%), protected cyclic (1,3;1,6)-β-glucan dodecasaccharide was obtained, together with by-products such as cyclic hexasaccharide and larger cyclic oligosaccharides, which were detected by MALDI-TOF-MS (see the ESI for details).

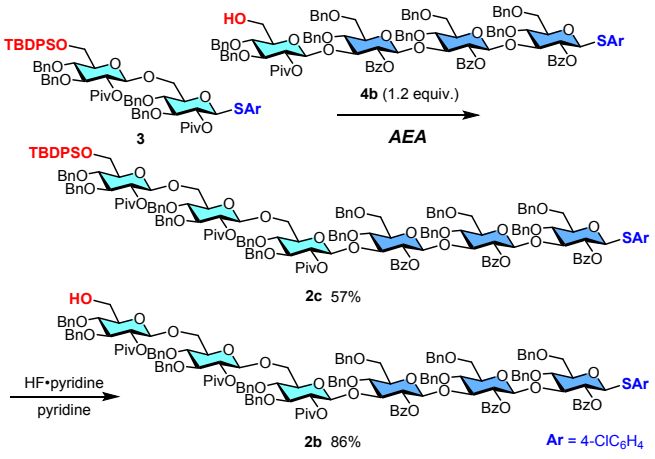
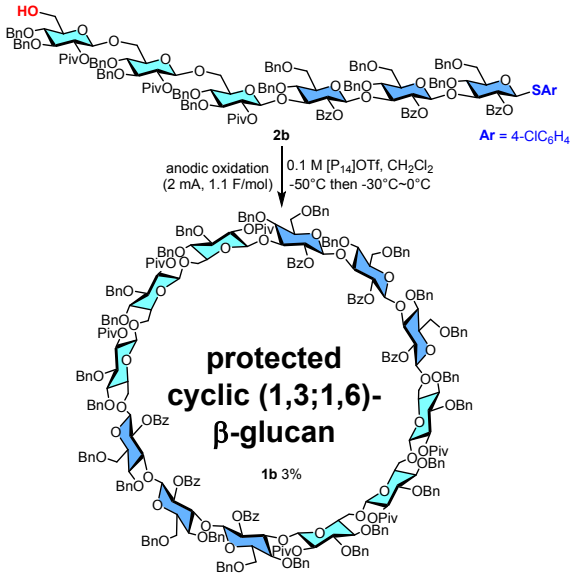


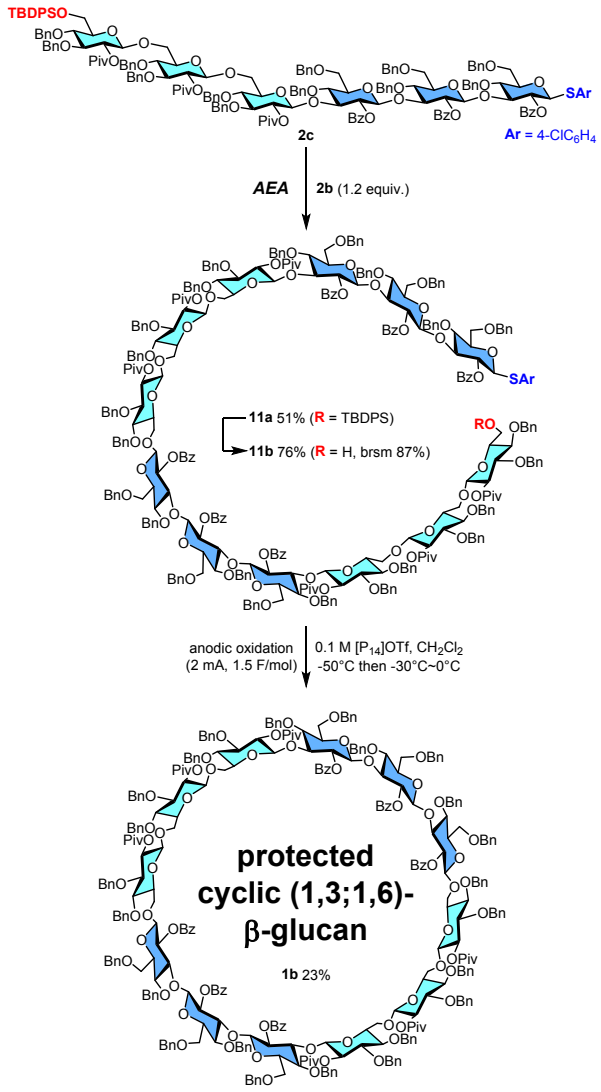
Fig. 6 Synthesis of semi-circular hexasaccharide **2b**.



Scheme 1 One-pot dimerisation-cyclisation process for the preparation of protected cyclic dodecasaccharide **1b**.

Synthesis of the protected cyclic dodecasaccharide via AEA

The results of the one-pot dimerisation–cyclisation process encouraged us to synthesise protected cyclic dodecasaccharide **1b** using AEA (Scheme 2). Two semi-circular hexasaccharide building blocks, **2b** and **2c** (1.2 equiv.), were assembled using AEA to prepare linear dodecasaccharide **11a** in 51% yield. The major by-product of the reaction was hydroxy sugar of **2c**, which was detected by MALDI-TOF-MS. The TBDPS group on the 6-OH of **11a** was then deprotected to obtain **11b** as a precursor of protected cyclic dodecasaccharide **1b**. Finally, the intramolecular electrochemical glycosylation of **11b** was performed at a low concentration (5 mM) to synthesise **1b** in 23% yield. The three-step yield of **1b** was ca. 10%, which was three times higher than that of the one-pot process shown in Scheme 1.



Scheme 2 Synthesis of protected cyclic dodecasaccharide **1b**.

Conclusions

We have synthesised the protected precursor of cyclic (1,3;1,6)-β-glucan dodecasaccharide, which is the core structure of the natural oligosaccharide isolated from *Bradyrhizobium japonicum* MTCC120. We designed a semi-circular hexasaccharide and its reactivity was confirmed by the electrochemical one-pot dimerisation−cyclisation process. Finally, the linear precursor of cyclic dodecasaccharide was prepared using AEA of linear hexasaccharides and subsequent electrochemical intramolecular glycosylation afforded the protected cyclic dodecasaccharide in a higher yield. Further optimisation of the electrochemical intramolecular glycosylation and global deprotection to obtain cyclic dodecasaccharide are in progress in our laboratory.

Experimental

General procedure for Automated Electrochemical Assembly and subsequent deprotection of TBDPS Group. The automated synthesis of linear dodecasaccharide **11a** was carried out in an H-type divided cell equipped with a carbon felt anode and a platinum plate cathode (20 mm×20 mm). In the anodic chamber were placed hexasaccharide building block **2c** (0.135 mmol, 405 mg), [P_{14}]OTf (0.76 mmol, 0.175 mL) and CH_2Cl_2 (3.9 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (0.20 mmol, 18 µL), [P_{14}]OTf (0.50 mmol, 0.12 mL) and CH_2Cl_2 (4.9 mL). The constant current electrolysis (2.0 mA) was carried out at -50°C with stirring until 1.1 F/mol of electricity was consumed. After the electrolysis, hexasaccharide building block **2b** (0.162 mmol, 450 mg) dissolved in CH_2Cl_2 (0.9 mL) was subsequently added by the syringe pump under an argon atmosphere at -50°C and then -30°C kept for 60 min. After elevation of the reaction temperature to -5°C, Et_3N (0.4 mL) was added, and the reaction mixture was filtered through a short column (4×3 cm) of silica gel to remove electrolyte Bu_4NOTf. Removal of the solvent under reduced pressure and the crude product was purified with silica gel chromatography (eluent: Hexane/EtOAc 3:1) and preparative recycling GPC (eluent: $CHCl_3$). Target linear dodecasaccharide **11a** was obtained in 51% isolated yield (0.069 mmol, 389 mg). Thus obtained **11a** was used as a starting material for the next step without detailed structural characterisation.

Linear dodecasaccharide **11a** (0.069 mmol, 389 mg) was dissolved in pyridine (0.53 mL) and the solution was cooled to 0°C. 70% HF•pyridine (0.10 mL) was added to the solution and the reaction mixture was stirred at 0°C to room temperature for 2 h. Conversion of **11a** was confirmed by TLC (Hexane/EtOAc 7:3) and aqueous sodium bicarbonate solution was added to quench the reaction. The aqueous solution was extracted with chloroform and the combined organic layer was washed with aqueous sodium bicarbonate solution and 1 N aqueous hydrochloric acid. The reaction mixture was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude product (430 mg). Thus-obtained crude product was purified by silica gel chromatography (eluent: Hexane/EtOAc 7:3) and **11b** (0.053 mmol, 284 mg) in 76% yield (87% conversion). 4-Chlorophenyl 3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-1-thio-β-D-glucopyranoside (**11b**); TLC (Hexane/EtOAc 7:3) R_f = 0.20; ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 2 H), 7.76−7.73 (m, 5 H), 7.52−7.48 (m, 2 H), 7.45 (d, J = 7.2 Hz, 1 H), 7.41−7.39 (m, 2 H), 7.36−6.99 (m, 141 H), 6.89−6.86 (m, 1 H),

5.08–5.05 (m, 2 H), 4.99–4.80 (m, 16 H), 4.74–4.14 (m, 55 H), 4.10–4.00 (m, 6 H), 3.90–3.82 (m, 5 H), 3.71–3.62 (m, 6 H), 3.60–3.16 (m, 41 H), 3.04–3.00 (m, 1 H), 2.17 (*pseudo*-t, *J* = 6.0 Hz, 1 H), 1.10 (s, 18 H), 1.08 (s, 9 H), 1.06 (s, 9 H), 1.05 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.3, 177.2, 177.1, 176.7, 176.6, 176.5, 176.4, 164.52, 164.47, 163.9, 138.58, 138.54, 138.51, 138.45, 138.35, 138.31, 138.28, 138.21, 138.18, 138.15, 138.11, 138.07, 138.01, 137.96, 137.87, 137.8, 137.7, 133.6, 133.28, 133.25, 133.22, 133.14, 133.0, 132.93, 132.90, 132.1, 129.78, 129.72, 129.65, 129.55, 129.48, 129.45, 129.38, 129.32, 129.25, 129.18, 129.15, 128.8, 128.7, 128.6, 128.53, 128.46, 128.35, 128.29, 128.24, 128.21, 128.18, 128.14, 128.03, 127.97, 127.94, 127.92, 127.91, 127.76, 127.73, 127.69, 127.63, 127.60, 127.56, 127.43, 127.41, 127.37, 127.35, 127.31, 127.26, 127.22, 127.21, 127.1, 127.0, 126.9, 101.5, 100.8, 100.7, 100.6, 100.5, 100.2, 99.8, 99.6, 99.5, 86.0, 83.1, 82.99, 82.95, 82.93, 82.85, 82.5, 82.4, 80.4, 79.1, 79.0, 78.78, 78.60, 77.73, 77.65, 77.63, 77.43, 76.4, 76.3, 75.98, 75.93, 75.89, 75.87, 75.72, 75.59, 75.56, 75.44, 75.15, 75.11, 75.03, 74.85, 74.77, 74.65, 74.61, 74.51, 74.37, 74.34, 74.27, 74.15, 74.12, 74.02, 73.96, 73.87, 73.79, 73.30, 73.25, 73.17, 73.11, 73.09, 72.82, 72.80, 72.52, 72.44, 72.22, 69.9, 69.21, 69.17, 69.10, 67.6, 61.8, 38.68, 38.62, 38.58, 27.24, 27.19, 27.13, 27.09, 26.99, 26.80, 26.76; MS (MALDI) *m/z* calculated for $C_{318}H_{341}ClKO_{72}S$ $[M+K]^+$ 5417.21; found 5417.67.

Electrochemical Intramolecular Glycosylation. The intramolecular glycosylation of linear dodecasaccharide **11b** was carried out in an H-type divided cell equipped with a carbon felt anode and a platinum plate cathode (10 mm×10 mm). In the anodic chamber were placed protected linear dodecasaccharide **11b** (0.028 mmol, 151 mg), $[P_{14}]OTf$ (0.74 mmol, 0.17 mL) and CH_2Cl_2 (5.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (0.14 mmol, 12 µL), $[P_{14}]OTf$ (0.50 mmol, 0.12 mL) and CH_2Cl_2 (5.1 mL). The constant current electrolysis (2.0 mA) was carried out at -50°C with stirring until 1.5 F/mol of electricity was consumed and then -30°C kept for 60 min. After elevation of the reaction temperature to -5°C, Et_3N (0.1 mL) was added to both chambers, and the reaction mixture was dissolved in $CHCl_3$ and washed with water to remove electrolyte $[P_{14}]OTf$. Thus-obtained organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product (160 mg). Silica gel chromatography (eluent: Hexane/EtOAc 3:1) and preparative recycling GPC (eluent: $CHCl_3$) afforded target protected cyclic dodecasaccharide **1b** in 23% yield (6.9 µmol, 36 mg). cyclobis-(1→6)-(3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl)-(1→3)-(2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-(2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-(2-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-glucopyranosyl) (**1b**); TLC (Hexane/EtOAc 3:1) R_f = 0.30; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (*pseudo*-t, *J* = 6.0 Hz, 4 H), 7.67–7.62 (m, 4 H), 7.59 (d, *J* = 7.2 Hz, 4 H), 7.46–7.43 (m, 6 H), 7.36–7.14 (m, 126 H), 7.05 (d, *J* = 6.0 Hz, 2 H), 5.09–5.00 (m, 12 H), 4.96–4.88 (m, 6 H), 4.74 (d, *J* = 7.8 Hz, 2 H), 4.70 (dd, *J* = 10.8, 3.0 Hz, 2 H), 4.66–4.61 (m, 6 H), 4.56–4.42 (m, 26 H), 4.38–4.25 (m, 12 H), 4.15 (d, *J* = 7.8 Hz, 2 H), 4.09 (*pseudo*-t, *J* = 9.0 Hz, 2 H), 4.02 (*pseudo*-t, *J* = 9.0 Hz, 2 H), 4.00–3.96 (m, 4 H), 3.79–3.74 (m, 4 H), 3.67–3.27 (m, 48 H), 3.21–3.15 (m, 4 H), 1.11 (s, 36 H), 1.08 (s, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 176.5, 176.4, 164.7, 164.4, 163.8, 138.7, 138.6, 138.43, 138.38, 138.2, 138.1, 138.04, 137.95, 137.91, 133.30, 133.24, 133.20, 129.82, 129.75, 129.5, 129.4, 129.3, 128.8, 128.61, 128.56, 128.43, 128.35, 128.25, 128.20, 128.15, 128.10, 128.05, 128.01, 127.96, 127.7, 127.6, 127.45, 127.39, 127.35, 127.31, 127.26, 127.21, 127.13, 127.0, 126.9, 126.8, 100.7, 100.5, 100.43, 100.35, 100.14, 99.3, 83.0, 82.9, 82.8, 82.7, 79.75, 79.66, 78.3, 78.2, 78.1, 77.6, 77.5, 76.3, 76.1, 75.6, 75.3, 75.2, 75.1, 74.85, 74.80, 74.72, 74.59, 74.54, 74.48, 74.33, 74.21, 73.84, 73.76, 73.3, 73.2, 73.1, 72.9, 72.2, 69.7, 69.15, 69.07, 67.7, 66.9, 38.65, 38.63, 38.59, 27.3, 27.1, 26.9; MS (MALDI) *m/z* calculated for $C_{312}H_{336}KO_{72}$ $[M+K]^+$ 5273.23; found 5273.04.

Author Contributions

A. Shibuya, N.S., T.I. and T.N. organized the research. A. Shibuya, Y.I., A. Saito, M.K., S.M., H.K. and R.A. synthesized and characterized compounds. A. Shibuya and T.N. principally wrote the manuscript according to the suggestion and discussion with all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors deeply acknowledge the Grant-in-Aid for Scientific Research on Innovative Areas: 'Middle Molecular Strategy' (No.2707) from the JSPS (No. JP15H05844), Grant-in-Aid for Scientific Research (C) from JSPS (No. JP19K05714), and JST CREST (No. JPMJCR18R4) for financial support.

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